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(54) Title: METHODS OF MODULATING COLLAGEN BIOSYNTHESIS BY USE OF NON-LASER LIGHT

(57) Abstract

The present invention provides a method of using non-coherent light to inhibit or stimulate collagen biosynthesis. The wavelength of the light determines whether stimulation or inhibition occurs.

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METHODS OF MODULATING COLLAGEN BIOSYNTHESIS BY USE OF NON-LASER LIGHT

INTRODUCTION

Technical Field

The present invention relates generally to the field of modulating collagen biosynthesis. Specifically, the invention relates to methods for modulating wound healing using non-coherent light sources. The particular wavelength employed determines whether collagen biosynthesis is stimulated or inhibited.

Background of the Invention

Collagen is the single most abundant protein in mammals, accounting for up to thirty percent of total protein. Collagen molecules, after being secreted by the cells, assemble into characteristic fibers responsible for the functional integrity of tissues such as skin, tendon, bone and cartilage. Collagen molecules contribute a structural framework to other tissues, such as blood vessels and most other organs. Crosslinks between adjacent molecules are a prerequisite for collagen fibers to withstand the physical stresses to which they are exposed. In human tissues, thirteen types of collagen are known. Of these different identifiable types, type I is the most abundant in skin, tendon, ligament, bone and cornea, where it makes up eighty to ninety percent of the total collagen connective tissue. Type I collagen is less dynamic in a full-grown individual than its counterparts in other organs

The extracellular matrix (ECM) of the various connective tissues, such as skin, consists of complex macromolecules, collagen, elastin and glycosaminoglycans (GAGs). The biosynthesis of these macromolecules involves several specific reactions that are often under stringent enzymatic control. The net accumulation of connective tissues is dependent upon the precise balance between the biosynthesis and degradation of the connective tissue components. Normally, collagen synthesizing activity is quite low in skin, tendon and other organs in which type I collagen is expressed, resulting in slow, almost negligible, turnover.

In many situations, however, increased or decreased rates of collagen biosynthesis are desirable. Decreased collagen biosynthesis is desired for treating various diseases that are associated with excessive collagen biosynthesis. For example, pulmonary fibrosis and liver cirrhosis are characterized by collagen deposition. Similarly, excessive collagen biosynthesis occurs in various forms of dermal fibrosis including systemic scleroderma, morphea, familial cutaneous collagenoma, and connective tissue nevi of the collagen type. Excessive collagen biosynthesis during wound healing can cause scarring, resulting in hypertrophic scars and keloid.

In various types of ophthalmic procedures, collagen biosynthesis can lead to an unsuccessful result. For example, collagen biosynthesis can cause failure of glaucoma treatment surgery due to undesirable complete healing of the wound through which intraocular pressure is to be released. Glaucoma encompasses a heterogeneous group of eye diseases characterized by a classical triad of symptoms: elevated intraocular pressure (IOP), optic nerve damage and progressive visual field loss. The increase of IOP is due to a decrease in the outflow of aqueous humor, the fluid in the anterior segment of the eye that is responsible for maintaining pressure balance for the entire eye. Glaucoma is the second most important cause of permanent blindness in the United States and the single most important cause of blindness among African Americans. Almost 80,000 Americans are blind from glaucoma; at least two million have the disease, while only half of those are probably aware of it. In addition to these facts, five to ten million Americans have elevated intraocular pressure which places them at risk for developing glaucoma. Surgical methods for treating glaucoma attempt to provide drainage channels to release aqueous humor and thus alleviate the intraocular pressure. For example, laser trabeculoplasty involves the controlled application of intense light to the trabecular meshwork in order to shrink its collagenous tissue and thereby open drainage channels for the aqueous humor. An alternative surgical technique used for treating glaucoma is glaucoma filtering surgery (GFS), in which a drainage channel is created for aqueous humor outflow from the anterior chamber to lower IOP (*See*, Shields, *Textbook of Glaucoma*, 3rd ed., Williams and Wilkins, Baltimore, 1992, Ch. 36, "Filtering Surgery"). Although these surgical methods have the potential to replace drug therapy permanently, their current high failure rate makes them unattractive

choices. After GFS, uncontrolled scarring of the surgical site usually occurs and the scar tissue frequently blocks the newly created drainage channel. Similarly, the initial decrease in IOP observed following laser trabeculoplasty is often lost after a few months or years.

Other ophthalmic procedures are also susceptible to failure due to the regressive wound healing response that is frequently encountered. Examples include keratorefractive surgery performed by means of radial keratotomy, excimer laser refractive keratoplasty, and holmium laser thermal keratoplasty. In all corneal surgery, collagen biosynthesis in response to the traumatic intervention can reverse the desired corneal radius change.

Another ophthalmic disease related to harmful proliferation of cells at a surgical site is proliferative vitreoretinopathy (PVR), a potentially blinding disease caused by the escape into and subsequent proliferation of retinal pigmented epithelial cells and other cell types in the vitreous cavity (posterior segment of the eye). This growth and differentiation of cells with the accompanying formation of an epiretinal membrane eventually can lead to a tractional distortion of the retina and eventual detachment of the retina. Various cell types implicated in the formation of PVR include: retinal pigmented epithelium (RPE), glial cells, fibroblasts, macrophages, and blood elements. The usual presentation of PVR is characteristic of the elements of wound healing. Cell type, presence of various growth and differentiation factors, as well as the generation of various extracellular matrix components (ECM) combine to promote the inappropriate formation of contractile membranes. Extracellular matrix components in epiretinal membranes have been analyzed and show collagen and fibronectin to be the major constituents.

Methods for inhibiting collagen biosynthesis would aid in the treatment of these conditions. Progression of diseases that are marked by excessive collagen biosynthesis could be slowed. Another benefit of such methods would be reduced scarring associated with wound healing, leading to a more cosmetically favorable result. Methods for inhibiting collagen biosynthesis would also improve the success of several types of ophthalmic surgery, including GFS.

Clinical research indicates that lasers are effective in preventing excessive collagen deposition in diseases characterized by active collagen synthesis. Keloid and other examples of hypertrophic scars have been treated with Nd:YAG laser with

reduction or suppression of the pro-collagen production by the fibroblast cell. However, lasers are extremely expensive to purchase, and require special training to handle and maintain. The high cost reduces the general availability of lasers to surgeons, including ophthalmic surgeons. Accordingly, there remains a need for a methods of inhibiting collagen biosynthesis that do not require expensive, complex lasers.

In other situations, an increase in collagen biosynthesis is desired, not a decrease. Active synthesis of collagen and other connective tissue components is essential for optimal wound healing, especially during the early stages of repair. Wound healing involves two distinct systems. First, the plasmin/plasminogen activator system is activated and plays a role in the degradation and removal of the damaged extracellular matrix by local pericellular proteolysis. Through this proteolytic activity, plasmin also modulates the growth of normal tissue and tissue damaged by trauma, infection or inflammation. The second system is the activated fibroblast system, which is involved in the replacement of damaged collagen by the synthesis of new collagen and the collagen matrix of GAGs.

Wound healing is a balance between these two systems: if proteolysis is minimal, less new collagen biosynthesis is required. Previous methods for modulating this balance has focused on the use of plasmin inhibitors, plasminogen activator inhibitors, or a combination of the two, to minimize proteolysis and tissue degradation. The rationale for use of these compounds is based upon their effect on isolated tissues or cell cultures. However, these *in vitro* results have not translated to *in vivo* efficacy. For the most part, these agents are not specific for connective tissue metabolism. Thus, their clinical efficacy is frequently compromised by toxicity that results in short- and long-term side effects. Therefore, new approaches are needed for the manipulation of connective tissue accumulation in physiological and pathological situations.

The present invention fulfills both the need for methods to inhibit collagen biosynthesis without the necessity of laser light, and the need for methods to stimulate biosynthesis.

Relevant Literature

It is known to use coherent radiation of the type produced by lasers for controlled thermal shrinkage of collagen tissue. In U.S. Patent No. 5,137,530, a system is disclosed for shape modification of the eye cornea using solid state lasers using holmium-doped YAG or YLF crystals. Such lasers are reportedly superior to gas lasers because of their relatively mechanically and optically simple and easy operation.

Coherent light is used to treat glaucoma, as disclosed, for example, in U.S. Patent No. 5,129,895. In that patent, a round fiber optic probe is used that directs focused light out of one side of the probe housing. The disclosed ophthalmic procedure involves forming a hole through the conjunctiva layer of a patient's eye, inserting the probe through the hole, and then pulsing the sclera with at least one pulse of laser light. Similarly, a keratoplasty system using a surgical laser that generates a wavelength energy range of about 1.80 to 2.55 microns is disclosed in U.S. Patent No. 5,374,265. The system is used to reshape the curvature of a cornea by shrinking the collagen using infrared radiation. Collagen connective tissue shrinkage in a keratoplasty system using laser coherent energy also is disclosed in U.S. Patent No. 4,976,709.

SUMMARY OF THE INVENTION

The present invention provides methods of modulating collagen biosynthesis. The methods involve focusing non-coherent light energy of a predetermined wavelength to a target site for a duration and periodicity sufficient to either inhibit or stimulate collagen biosynthesis at the target site. Whether collagen biosynthesis is stimulated or inhibited depends upon the wavelength of the non-coherent light energy. Collagen biosynthesis is stimulated by wavelengths in the red and near-infrared portion of the electromagnetic spectrum, while longer wavelengths inhibit collagen biosynthesis.

The methods for inhibiting collagen biosynthesis are useful for treating collagen connective tissue disorders. Non-coherent light energy of a predetermined wavelength is focused to an area of excessive collagen biosynthesis for a duration and periodicity sufficient to inhibit the collagen biosynthesis. Among the conditions treatable using the claimed methods are pulmonary fibrosis, liver cirrhosis, systemic

scleroderma, morphea, familial cutaneous collagenoma, connective tissue nevi of the collagen type, hypertrophic scars and keloid.

The methods for inhibiting collagen biosynthesis are also useful in laser or surgical treatment of glaucoma, where a wound site is created by forming a hole through the conjunctive layer of a patient's eye to release intraocular pressure. Non-coherent light energy of a predetermined wavelength is then focused to the wound site for a duration and periodicity sufficient to inhibit collagen biosynthesis at the wound site. This prevents undesirable complete healing of the wound, which would otherwise block the desired release of excess eye pressure. Other types of eye surgery are also facilitated by the claimed methods.

Also provided are methods for stimulating collagen biosynthesis using a non-coherent light source. Non-coherent, non-laser light energy is directed through a filter to obtain light energy having a wavelength in the red or near-infrared range. The light is then focused on a target site for a duration and periodicity sufficient to stimulate collagen biosynthesis at the target site.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides devices and methods for inhibiting and stimulating collagen biosynthesis. The inhibition or stimulation is accomplished by focusing non-coherent light energy to a predetermined wavelength at a target site where inhibition or stimulation of collagen biosynthesis is desired. The particular wavelength employed determines whether collagen biosynthesis is stimulated or inhibited.

Definitions

An "absorption coefficient" of a substance is a measure of the fraction of incident light that is absorbed when light is passed through the substance. The absorption coefficient (typically in units of cm^{-1}) varies with the nature of the absorbing substance and with the wavelength of the light.

"Collagen" as used herein refers to any of the several types of collagen.

Collagen biosynthesis is said to be "inhibited" when cells treated with the claimed methods secrete collagen at a rate that is less than about 70% of that of untreated cells. Preferably, treated cells secrete collagen at a rate that is less than about 50%, and more preferably less than about 30% of the rate at which untreated

cells secrete collagen.

Collagen biosynthesis is said to be "stimulated" when cells treated with the claimed methods secrete collagen at a rate that is greater than about 110% of the rate at which untreated cells synthesize collagen. Preferably, treated cells secrete collagen at a rate that is about 150%, and more preferably greater than about 200% greater than that of untreated cells.

"Monochromatic" light is of one wavelength or a narrow range of wavelengths. If the wavelength is in the visible range, monochromatic light will be of a single color. As used herein, "monochromatic" refers to light that has a bandwidth of less than about 100 nm. More preferably, the bandwidth will be less than about 10 nm, and most preferably less than about 1 nm.

"Non-coherent light energy" is light that is non-laser. Unlike laser light, which is characterized by having its photon wave motions in phase, the wave motions of the photons that make up non-coherent light are out of phase.

Detailed Description

Methods and devices for modulating collagen biosynthesis are provided. The methods involve focusing non-coherent light energy of a predetermined wavelength to a target site where collagen biosynthesis can potentially occur. Depending upon the particular wavelength employed, collagen biosynthesis is either inhibited or stimulated. Generally, wavelengths in the red and near-infrared portion of the electromagnetic spectrum stimulate collagen biosynthesis, while longer wavelengths inhibit collagen biosynthesis.

To inhibit collagen biosynthesis, light energy of a wavelength greater than about 1.0 μm, preferably about 1.06 μm, is delivered to the target site for a time period sufficient to accomplish the inhibition. Stimulation of collagen biosynthesis occurs when light energy at 640 nm or 900 nm is delivered to a target site for a time period sufficient to accomplish the stimulation.

The optimal wavelength within these ranges is influenced by whether the light energy must pass through overlying tissue before reaching the target site. In such cases where the target site is shielded by other tissue, the light energy is transmitted through the shielding tissue and focused on the target site so that the desired energy level is obtained at the target site. Because transmission of light through tissue is

highly wavelength-specific, one should choose a wavelength that is not highly absorbed by overlying tissue.

To modulate collagen biosynthesis, an amount of light energy of an appropriate predetermined wavelength is delivered to the target site that is sufficient to have the desired stimulatory or inhibitory effect. The amount of energy delivered to a target site is a function of several factors, including the output of the light source, the energy flux at the target site as determined by the source output and the degree of focusing achieved by the light delivery apparatus, and the time period for which the target site is exposed to the light energy. Another factor, discussed below, is the nature of any tissue overlying the target site.

The appropriate combinations of energy flux and time period for a desired effect on collagen biosynthesis can be determined empirically. For example, one can determine the effect on collagen biosynthesis of irradiating cells growing in culture, preferably in monolayers, with light energy of a given wavelength, energy flux, and time period.

In general, the desired energy density delivered to the target site is between about 1.0×10^3 and 1.6×10^3 Joules cm^{-2}. Preferably, the energy density at the target site is about 1.1×10^3 Joules cm^{-2}. For most applications, the amount of energy delivered to the target site should be sufficient to modulate collagen biosynthesis, but should not be so great as to cause a significant decrease in cell proliferation. For example, 1.7×10^3 Joules cm^{-2} of 1064 nm laser light is known to inhibit fibroblast proliferation. Thus, an energy that is between about 1.1×10^3 and about 1.7×10^3 Joules cm^{-2} is preferred.

To achieve the desired energy density, the light energy is delivered to the target site for a sufficient time period. The time period necessary depends on the energy flux delivered to the target site by the light delivery apparatus. The light can be delivered as a single pulse, or as a multiplicity of pulses. Often, the use of short pulses is preferred, as the shorter pulses cause less undesirable heating of the tissues surrounding the target site than does a single pulse of longer duration. Preferably, a higher-power shorter-duration pulse is used, rather than a low-power long-duration pulse. Typical pulse durations are between about 0.01 and 1.0 seconds, most preferably about 0.1 seconds.

Light Delivery Apparatus

Many types of non-laser light sources are suitable for producing the non-coherent light that is used in the claimed methods. For example, one can employ polychromatic light sources such as heated lamp filaments or gas filled vacuum tubes. Commercially available light sources are discussed in, for example, LaRocca, A., "Artificial Sources," In *Handbook of Optics*, Vol. I, Ch. 10, Bass et al., eds., McGraw-Hill, New York, 1995, pp. 10.3-10.50, and references cited therein

If a polychromatic light source is used, the light energy is preferably made monochromatic or nearly monochromatic by suitable methods known to those of skill in the art. For example, one can direct the polychromatic light through a filter or a series of filters that transmits only light of the desired wavelength or range of wavelengths. Suitable filters are described in, for example, Dobrowolski, J.A., "Optical Properties of Films and Coatings," In *Handbook of Optics*, Vol. I, Ch. 42, Bass *et al.*, eds., McGraw-Hill, New York, 1995, pp. 42.3-42.130, and references cited therein. Bandpass filters are reviewed, for example, in Macleod, H.A., *Thin film Optical Filters*, McGraw-Hill, New York, 1986; "Metal-dielectric Interference Filters," in *Physics of Thin Films*, Hass *et al.*, eds., Academic Press, New York, 1977, vol. 9, pp. 73-144; Barr, "The Design and Construction of Evaporated Multilayer Filters for Use in Solar Radiation Technology," in *Advances in Geophysics*, Drummond, ed., Academic Press, New York, 1970, pp. 391-412).

In a preferred embodiment, a monochromatic or nearly monochromatic light source is used. By choosing a light source that emits monochromatic or nearly monochromatic light, the need to filter or focus the light to the desired wavelength is eliminated. Several types of monochromatic or nearly monochromatic light sources are known to those of skill in the art. *See, e.g.*, LaRocca, *supra.*, for types and sources of monochromatic light sources.

Light-emitting diodes (LEDs) are a most preferred light source for use in the claimed invention. LEDs are described, for example, in Haitz *et al.*, "Light-Emitting Diodes," In *Handbook of Optics*, Vol. I, Ch. 12, Bass, M., ed., McGraw-Hill, New York, pp. 12.1-12.39. Both surface and edge emitters are commercially available, in continuous and pulse-operated modes. Commercially available LEDs that are useful in the claimed methods emit wavelengths of 830, 904, 1060, 1300, and 1550 nm. The 830 and 904 nm LEDs are useful for stimulating collagen

biosynthesis, while the 1060, 1300, and 1550 nm LEDs are appropriate for inhibition.

Light energy used in the claimed methods is preferably collimated, in addition to being of a predetermined wavelength or range of wavelengths. Collimation can be achieved by any of several methods known to those of skill in the art. For example, passing light through fiber optics of various core diameters will achieve collimation. Suitable fiber optic instrumentation is available from EG&G Opto-Electronics of Salem, Mass. Optical fibers are described, for example, in Brown, T.G., "Optical Fibers and Fiber-Optic Communications," In *Handbook of Optics*, Vol. II, Ch. 10, Bass, M., ed., McGraw-Hill, New York, pp. 10.1 *et seq.*

The light energy is focused to the target site as a spot having a diameter that is appropriate for the particular treatment being undertaken. Where inhibition of collagen biosynthesis in a relatively small area is used, the light is focused to a correspondingly small spot at the target site. Typically, the light energy is focused to a spot with a diameter in the range of about 0.25 to about 2.0 millimeters. The focusing step also concentrates the light to an energy flux that is sufficient to achieve the desired inhibition when delivered to the target site for an appropriate period of time.

Methods for focusing light to achieve a desired energy flux and spot diameter are known to those of skill in the art. For example, a focusing lens made of glass, silica, or refractory material such as diamond or sapphire is commonly employed. In a preferred embodiment, the focusing lens directs the non-coherent light energy to an optical fiber of an appropriate core diameter and composition. For example, a 100 μm diameter low-OH silica optic fiber is appropriate. A fiber that produces a relatively low amount of transmission loss is preferred, preferably less than about 15% loss over a length of up to ten meters. The fiber is typically mounted in a shaft for delivery of the non-coherent light energy to the tissue. The output end of the shaft is preferably fitted with an output tip that can directly contact the tissue while maintaining the delivery end of the fiber a desired distance away from the tissue. This distance can be varied by substituting a longer or shorter output tip, or by slidably adjusting the position of the output tip on the shaft.

For some applications, it is desirable to use an output tip that directs the non-coherent focused light out of its side, rather than through the end of the fiber. Means

for accomplishing this are known to those of skill in the art. For example, US Patent No. 5,129,895 describes the use of a reflecting surface at the end of the fiber combined with lens action on the fiber side.

The invention also provides an apparatus for modulating collagen biosynthesis according to the methods described herein. The apparatus comprises a source of non-coherent light energy, a means for collimating the light energy generated by the light source, and a means for focusing the collimated light energy to a target site. The apparatus delivers sufficient light energy to the target site to modulate collagen biosynthesis.

Therapeutic Applications

The claimed methods for modulating collagen biosynthesis are useful in treating many conditions. Depending upon the condition being treated, either inhibition or stimulation of collagen biosynthesis may be desired.

The methods for inhibiting collagen biosynthesis are useful in situations where collagen biosynthesis is excessive or otherwise undesirable. One application is the prevention or reduction of scarring during wound repair. Scarring, such as hypertrophic scars and keloid, is often the result of excessive collagen biosynthesis during wound healing. To obtain a more favorable result following cosmetic or other surgery, the practitioner directs non-coherent light of a predetermined wavelength to the area of the wound. Wavelengths greater than about 1000 nm are effective at inhibiting collagen biosynthesis, in particular 1060 nm is effective. The light energy is focused on the target site for a period and duration sufficient to inhibit collagen biosynthesis at the site. The time and period will vary depending upon the energy delivered by the light apparatus. For treatment of wounds that are larger than the diameter of the light spot delivered to the target site by the apparatus, the clinician can deliver the light energy to a plurality of target sites in the wound area.

The invention also finds use in various types of ophthalmic applications. For example, collagen biosynthesis can cause failure of glaucoma filtering surgery (GFS) due to undesirable complete healing of the wound through which intraocular pressure is to be released. To treat glaucoma, a wound site is created by forming a hole through the conjunctive layer of a patient's eye to release intraocular pressure. non-coherent light energy of a predetermined wavelength is then focused to the wound site

for a duration and periodicity sufficient to inhibit collagen biosynthesis at the wound site. If necessary, the collagen inhibition protocol can be repeated to maintain suppression of collagen biosynthesis.

The invention is also useful for preventing the regressive wound healing response that is frequently encountered in keratorefractive surgery performed by means of radial keratotomy, excimer laser refractive keratoplasty, or holmium laser thermal keratoplasty. In all corneal surgery, collagen biosynthesis in response to the traumatic intervention can reverse the desired corneal radius change. To prevent these undesirable effects, the clinician focuses light energy of a wavelength appropriate for inhibiting collagen biosynthesis to the area treated by the surgical or laser procedure.

Similarly, the claimed methods for inhibiting collagen biosynthesis are useful for treating various acquired and inherited disorders of connective tissue. For example, pulmonary fibrosis and liver cirrhosis are characterized by collagen deposition. Thus, use of the invention to prevent collagen biosynthesis can prevent progression of these diseases. Similarly, excessive collagen biosynthesis occurs in various forms of dermal fibrosis including systemic scleroderma, morphea, familial cutaneous collagenoma, and connective tissue nevi of the collagen type.

To prevent progression of these diseases, non-coherent light energy of a wavelength appropriate for inhibiting collagen biosynthesis is delivered to areas where excessive collagen biosynthesis is occurring. In situations where the target site is not readily accessible to the light apparatus, one can incorporate the light delivery system into an endoscope. Endoscope systems for use with light of various wavelengths are known to those of skill in the art.

The invention also provides methods for stimulating collagen biosynthesis. These methods are also useful in the clinical setting. For example, stimulation of collagen biosynthesis is often desirable in the early stages of wound healing. The procedures employed are similar to those used for inhibiting collagen biosynthesis, except for the wavelength of light delivered to the target site. To stimulate collagen biosynthesis, one delivers light in the red or near-infrared range of the electromagnetic spectrum to the target site. For example, light energy at 640 nm or 900 nm stimulates collagen biosynthesis when delivered to a target site at specific energy densities and durations.

To enhance wound healing, collimated light energy of an appropriate wavelength is delivered to the wound at an energy density sufficient to stimulate collagen biosynthesis. The light energy can be delivered as a single pulse, or more preferably, as a series of pulses. The use of short pulses reduces the likelihood of undesired heating of the tissue. Preferably, the light energy delivered is sufficient to stimulate collagen biosynthesis, but is insufficient to inhibit cell proliferation.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications and patent documents referenced in this application are incorporated herein by reference.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

What is claimed is:

1. A method of modulating collagen biosynthesis, the method comprising focusing non-coherent light energy of a predetermined wavelength to a target site for a duration and periodicity sufficient to inhibit or stimulate collagen biosynthesis at the target site.

2. The method according to Claim 1 wherein collagen biosynthesis is inhibited.

3. The method according to Claim 2 wherein the predetermined wavelength is between about one micron and about two microns.

4. The method according to Claim 3 wherein the predetermined wavelength is about 1.06 microns.

5. The method according to Claim 1 wherein collagen biosynthesis is stimulated.

6. The method according to Claim 5 wherein the predetermined wavelength is in the red or near-infrared range.

7. The method according to Claim 6 wherein the predetermined wavelength is between about 640 and about 900 nm.

8. The method according to Claim 6 wherein the predetermined wavelength is about 770 nm.

9. The method according to Claim 1, wherein the light is collimated prior to contacting the target site.

10. The method according to Claim 1, wherein the non-coherent light energy is produced by a polychromatic light source and the predetermined wavelength is achieved prior to contacting the target site.

11. The method according to Claim 10, wherein the light source is a heated lamp filament or a polychromatic gas filled vacuum tube.

12. The method according to Claim 10, wherein the predetermined wavelength is achieved by passing the light through a filter.

13. The method according to Claim 1, wherein the non-coherent light energy is produced by a monochromatic or near-monochromatic light source.

14. The method according to Claim 13, wherein the light source is a monochromatic gas filled vacuum tube, a light-emitting diode, or a semiconductor diode.

15. The method according to Claim 1, wherein the light energy is focused to the target site for a period of time sufficient to deliver an energy density of about 1.0×10^3 Joules cm^{-2} to about 1.6×10^3 Joules cm^{-2} to the target site.

16. The method according to Claim 15, wherein the energy density delivered to the target site is about 1.1×10^{-3} Joules cm^{-2}.

17. The method according to Claim 1, wherein the light energy is focused at the target site to a spot with a diameter in the range of about 0.25 to 2.0 millimeters.

18. The method according to Claim 1, wherein the focused light energy is delivered to the target site as one or more pulses.

19. The method according to Claim 18, wherein each pulse has a duration of about 0.01 to about 1.0 second.

20. The method according to Claim 19, wherein each pulse has a duration of about 0.1 seconds.

21. The method according to Claim 18, wherein the focused light energy is delivered to the target site as one pulse.

22. A method for inhibiting collagen biosynthesis using a non-coherent light source, the method comprising the steps of:

directing a non-coherent light through a filter to obtain light energy having a wavelength greater than about 1.0 micron; and

focusing the light on a target site for a duration and periodicity sufficient to inhibit collagen biosynthesis at the target site.

23. A method for treating collagen connective tissue disorders, comprising focusing non-coherent light energy of a predetermined wavelength to an area of excessive collagen biosynthesis for a duration and periodicity sufficient to inhibit the collagen biosynthesis.

24. The method according to Claim 23, wherein the collagen connective tissue disorder is selected from the group consisting of: pulmonary fibrosis, liver cirrhosis, systemic scleroderma, morphea, familial cutaneous collagenoma, connective tissue nevi of the collagen type, hypertrophic scars and keloid.

25. The method according to Claim 23, wherein the focused energy is delivered to the target site as one or more pulses.

26. A method for inhibiting regressive wound healing, comprising focusing

non-coherent light energy of a predetermined wavelength to the area of a wound for a duration and periodicity sufficient to inhibit collagen biosynthesis.

27. The method according to Claim 26, wherein the focused light energy is delivered to the wound within a predetermined time after the wound is inflicted.

28. The method according to Claim 27, wherein the predetermined time is about one hour.

29. The method according to Claim 26, wherein the predetermined wavelength is between about one micron and about two microns.

30. The method according to Claim 29, wherein the predetermined wavelength is about 1.06 microns.

31. The method according to Claim 26, wherein the wound is inflicted by a corneal surgery procedure selected from the group consisting of: radial keratotomy, excimer laser refractive keratoplasty, and holmium laser thermal keratoplasty.

32. The method according to Claim 26, wherein the wound is inflicted by a surgery selected from the group consisting of: plastic surgery, cataract removal, and corneal transplant.

33. The method according to Claim 26, wherein the focused energy is delivered to the wound as one or more pulses.

34. The method according to Claim 26, wherein the duration of each pulse is less than about one second.

35. A method for treating glaucoma, comprising the steps of:

creating a wound site by forming a hole through the conjunctive layer of a patient's eye to release intraocular pressure; and

focusing non-coherent light energy of a predetermined wavelength to the wound site for a duration and periodicity sufficient to inhibit collagen biosynthesis at the wound site.

36. The method according to Claim 35, wherein the predetermined wavelength is greater than about 1.0 microns.

37. The method according to Claim 36, wherein the predetermined wavelength is about 1.06 microns.

38. A method for stimulating collagen biosynthesis using a non-coherent light source, the method comprising the steps of:

directing a non-coherent light through a filter to obtain light energy

having a wavelength in the red or near-infrared range; and

focusing the light on a target site for a duration and periodicity sufficient to stimulate collagen biosynthesis at the target site.

39. The method according to Claim 38, wherein the focused energy is delivered to the target site as one or more pulses.

40. A method for enhancing wound healing, comprising focusing non-coherent light energy of a predetermined wavelength to a wound for a duration and periodicity sufficient to stimulate collagen biosynthesis.

41. The method according to Claim 40 wherein the focused light energy is delivered to the wound within a predetermined time after the wound is inflicted.

42. The method according to Claim 41 wherein the predetermined time is about one hour.

43. The method according to Claim 40 wherein the predetermined wavelength is in the red or near-infrared range.

44. The method according to Claim 43 wherein the predetermined wavelength is between about 640 nm and about 900 nm.

45. The method according to Claim 40 wherein the focused energy is delivered to the wound as one or more pulses.

46. The method according to Claim 45 wherein the duration of each pulse is less than about one second.

47. An apparatus for modulating collagen biosynthesis comprising:

a) a source of non-coherent light energy;

b) a means for collimating the light energy generated by the light source; and

c) a means for focusing the collimated light energy to a target site; wherein sufficient light energy is delivered to the target site to modulate collagen biosynthesis.

INTERNATIONAL SEARCH REPORT

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PCT/US97/03787

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 17/36; 19/00
US CL :128/898; 606/3, 6; 607/89
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 606/3, 6; 607/89

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,854,320 A (DEW et al) 08 August 1989, entire document.	1-47
A	US 4,976,709 A (SAND) 11 December 1990, entire document.	1-47
Y	US 5,129,895 A (VASSILIADIS et al) 14 July 1992, entire document.	1-47

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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